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TUTORIAL

Improving pharmacometrics analysis efficiency using DataCheQC: An interactive, Shiny-based app for quality control of pharmacometrics datasets

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Abstract

DataCheQC is an interactive application based on the R Shiny framework developed for the purposes of performing quality control (QC) checks on pharmacometric datasets, and thereby supporting the implementation of model-informed drug development. Features include visual inspection of variables and data entries for errors and/or anomalies, and ensuring structural integrity through comparison with a dataset specification file. The app, which requires no programming knowledge to operate, allows the user to collect all findings into a summary report downloadable directly from the app itself. The source code for the app is freely available on GitHub under an open-source license (https://github.com/DotanOr/DataCheQC) and can also be accessed online (https://dotanor.shinyapps.io/DataCheQC/).

INTRODUCTION

The process of pharmacometrics dataset preparation usually starts with the pharmacometrician providing the data specification to a programmer.[1] The programmer then prepares the requested dataset and often performs code-level checking. Before the dataset is delivered, the programmer should make assurances that the deliverable matches the initial request. Quality control (QC) is the process of ensuring accuracy, consistency, and error prevention. In the scope of pharmacometric data preparation, this includes various checks, such as identifying missing records, validating formatting and units, and adhering to the data specifications.[2–4]

However, QC of incoming data, which can often be frequent during ongoing study, can potentially be a time-consuming process.[5] Therefore, a streamlined and automated process of identifying and reporting potential issues in the data can be beneficial to the conduct of pharmacometrics analyses.

A POSSIBLE SOLUTION IN SHINY

One way to ameliorate the QC process is to reduce the busywork required to check each new dataset by creating a system that is both interactive and data-agnostic (i.e., can work with many different datasets without requiring additional configuration). As has been shown previously, a highly effective solution for improving the pharmacometrics workflow is to use programmatic tools[6] and interactive apps, such as those based on the Shiny R package.[7–11] The Shiny framework enables creation of web apps that are simple to use and customize, incorporating both front-end (visual design and interactivity) and back-end (calculations and database manipulation) capabilities. These

apps enable the user to take advantage of the robust library of packages for data science and statistical analyses offered by the R language.

REQUIREMENTS FOR A SHINY QC APP

An automated QC app based on the R Shiny framework can be an agile, versatile, and convenient solution to facilitate QC processes. In order to do so, such an app should perform the following typical tasks:

- Matching the dataset to the data specification file[3,4,12,13]
- Checking for missing or unavailable (NA) data entries:
  - Confirming that the variables have correct data types and units
  - Ensuring number of unique data values and their derivation matches data specification
- Data visualization to detect outliers and/or missing values[3,4,12,14]:
  - Comparing protocol-defined nominal times (NTs) with actual observation or event times relative to the first drug administration to detect aberrations
  - Reviewing individual profiles to detect missing or anomalous data entries
  - Checking covariate distributions and correlations
  - Reviewing tabulated summaries to examine attributes of the dataset, such as number of participants per study, amount of missing or unquantifiable samples, and the central tendencies of covariates.

Completing these tasks should be carried out using the following recommended workflow:

1. Loading of the selected dataset in to the app.
2. Comparing the raw dataset with the data specification file to detect any discrepancies.
3. Conducting visual checks and review summary statistics, paying attention to any outliers or errors.
4. Collecting any and all findings into a QC Report.

To fully leverage app functionalities, a standardized dataset structure needs to be assumed. Schmidt et al.[15] proposed the "generalized dataset" as a solution for a pharmacometrics dataset format which is compound- and indication-independent, not specific to a particular type of pharmacometrics analysis, and not tied to a specific nonlinear mixed-effect (NLME) software. The format can handle various types of data, such as demographics, pharmacokinetics (PKs), and pharmacodynamics (PDs), and requires minimal manipulation of Clinical Data Interchange Standards Consortium[16] data to compile a resulting dataset. The generalized dataset can be seamlessly converted to an NLME dataset suitable for analysis in NONMEM[17] and Monolix[18] using available tools.[19] Authors' positive experience with generalized dataset across different drug development programs and organizations influenced the choice of this particular format. Requirements for the datasets to be used with QC app are detailed in Table 1.

DATACHEQC SHINY APP

Applying the abovementioned principles has led to the creation of a Shiny app, "DataCheQC." The app also makes use of R packages that have been developed specifically for handling and analyses of pharmacometrics datasets, such as IQR Tools[19] and xgxr.[20]

Each aspect of the app is explained and made more accessible to the user by the presence of tooltips. These are messages that appear when the user hovers on certain buttons or the info icon (small white "i" against a black circle background; Figure 1).

TABLE 1 Required variables for the general dataset.

Name	Description	Type
USUBJID	Unique subject identifier	String
COMPOUND	Name of the investigational compound	String
TRTNAME	Name of actual treatment given to subject	String
TIMEUNIT	Unit of all numeric time in the dataset	String
NT	Nominal time of event relative to the first dose administration	Numeric
TIME	Actual time of event relative to the first dose administration	Numeric
TYPENAME	Unique type of event (e.g., dose, PK, PD, continuous covariate, categorical covariate, adverse event, concomitant medication)	String
NAME	Unique short name of event	String
VALUE	Value of event defined by NAME	Numeric
VALUETXT	Text version of value (if applicable)	String
UNIT	Unit of the value reported in the VALUE column	String
ROUTE	Route of administration	String

Abbreviations: NT, nominal time; PD, pharmacodynamic; PK, pharmacokinetic.

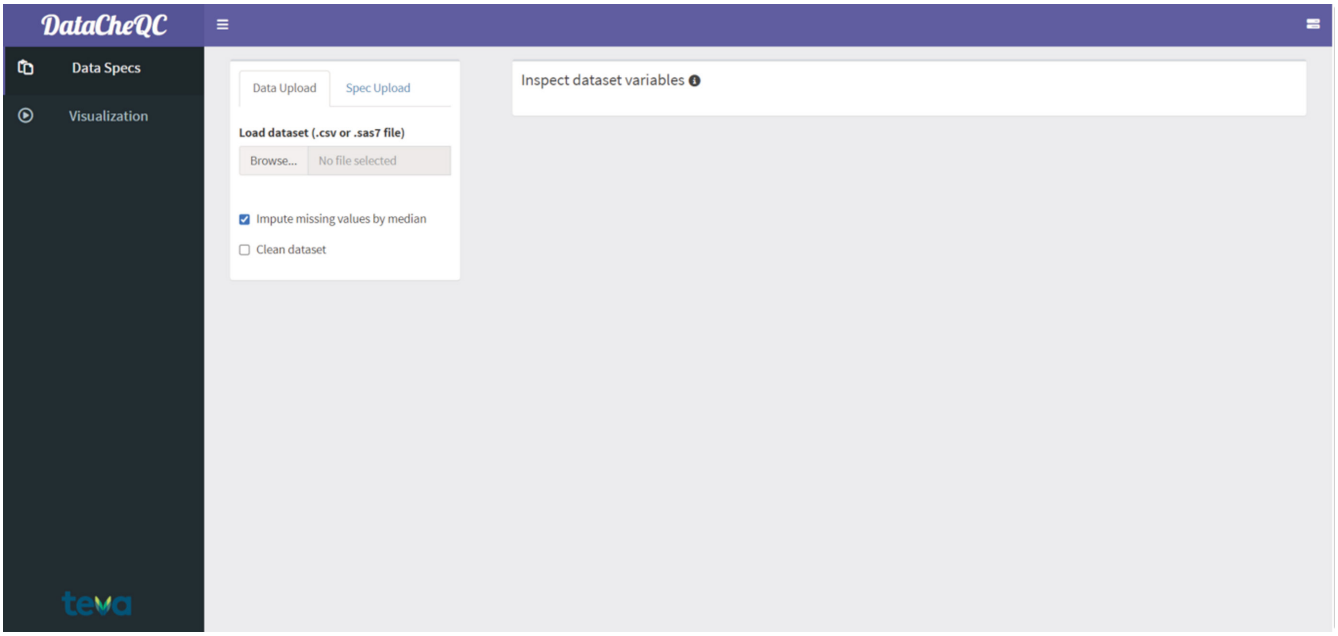


FIGURE 1 The DataCheQC App. The user can upload a dataset on the app's landing page by clicking the "Browse..." button and selecting its location in their file system. It is also possible to impute or clean the dataset by clicking on the appropriate checkboxes, which can be applied both before and after file selection. Info icons next to the various functions reveal an explanation of features.

Along with R code, the app incorporates some HTML, CSS, and JavaScript elements for visual styling and improved performance.

The following section of the paper will serve as a detailed, step-by-step explanation and demonstration of the app and its functionalities.

UPLOADING THE DATASET

The QC process begins when the user uploads the dataset into the app via the "Load Dataset" input field, which accepts both .csv and .sas7bdat files, as long as they fit the abovementioned minimal required dataset format. An example dataset with dummy data is used throughout this demonstration and is provided in the Supplementary Material. If the uploaded dataset does not match the required format, the app will notify the user of the missing variables (Figure S1).

Datasets that are uploaded into the app are not stored permanently on the Shiny server, and only exist as temporary files in the system. The temporary files expire when the user session ends, either due to server time-out or when exiting the app webpage. Similarly, dataset manipulation performed in the app will not alter the original file and instead will operate on the temporary local version. This is an important feature, as the app maintains dataset integrity.

The file upload process can often take between a few seconds to a few minutes, depending on the size of the dataset. After a successful upload, the app will attempt to automatically locate and identify various key variables in the dataset, including the dosing records, observations and covariates (Figure 2). For covariates, the app checks for common names (e.g., weight, gender, and age), and determines whether they are continuous or categorical. This distinction can also be defined in the TYPENAME variable. In addition, the app checks whether or not covariates are time-dependent. For each PD observation, a continuous "Baseline" covariate is automatically created to facilitate comparisons of the dynamics of those observations over time. The values for this baseline variable are determined according to variable BASE, where BASE = 1. In cases where BASE is not included in the dataset, the values are derived from entries where protocol-defined relative NT is equal to 0. The user may also choose to impute missing values or perform basic cleaning functions on the dataset by selecting the appropriate checkboxes. Once all relevant variables have been identified, the app will begin to generate an interim analysis dataset which is more suitable for subsequent exploratory analyses.

As the abovementioned processing of the dataset can take some time, the app utilizes asynchronous/parallel computation via the Future[21] and Promises[22] R packages. Parallelization enables multiple users to work with the app concurrently on the same Shiny server and allows the user to start with comparisons of the unprocessed dataset against the specification file.

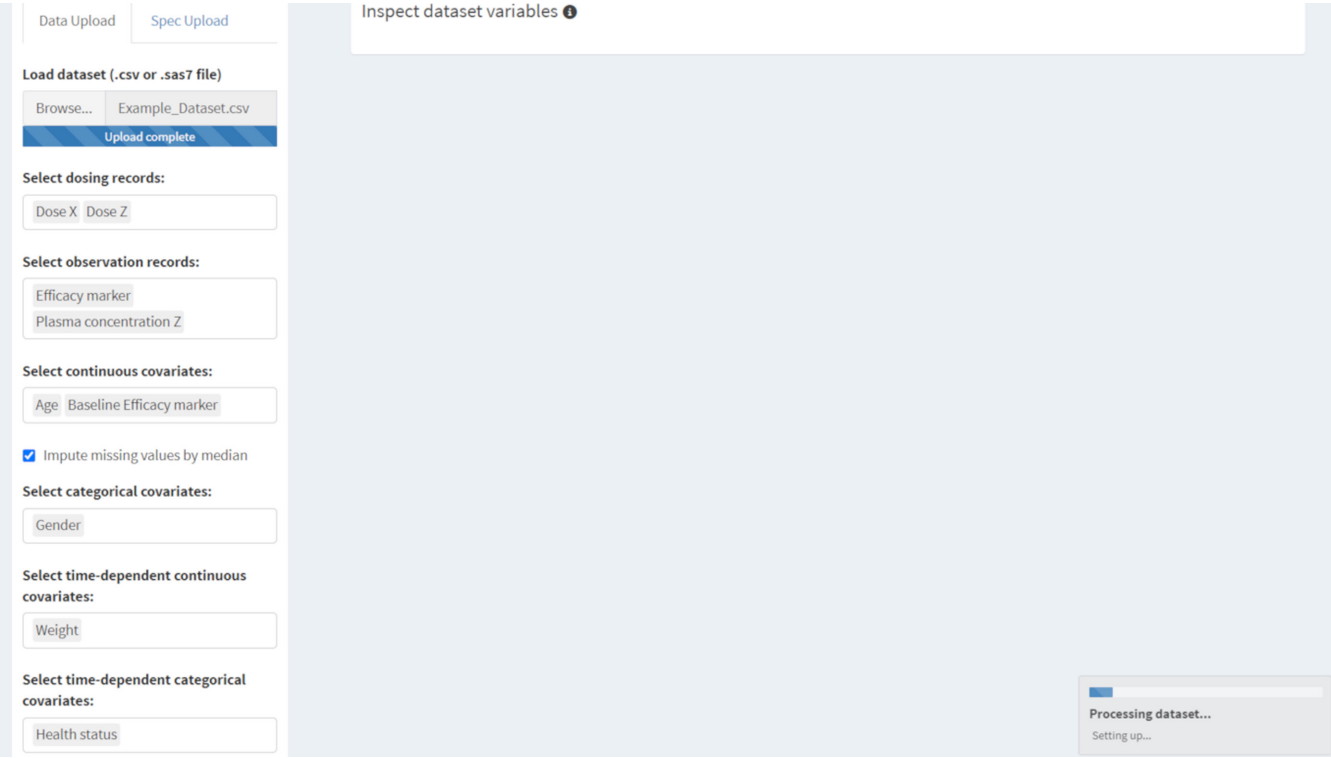


FIGURE 2 Loading the dataset. Once a dataset has been uploaded, the app will attempt to automatically detect the dosing, observations, and covariates. A notification at the bottom right of the screen will inform the user of the dataset processing status.

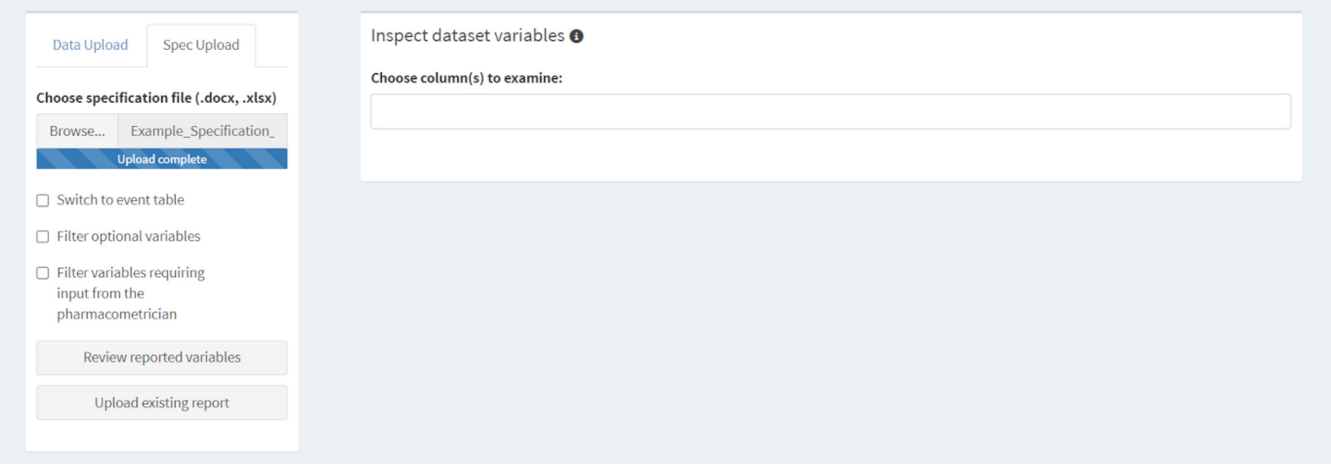


FIGURE 3 Uploading the specification file. The user can upload the specification file by clicking on the "Spec Upload" tab and using the file selection input. After the specification file has been loaded into the app, the user can select variables to examine on the right, while additional options are available on the left-hand side.

COMPARISON WITH DATA SPECIFICATIONS

The user uploads the relevant data specification file by switching to the "Spec Upload" tab and using the "Choose specification file" input field (Figure 3). The specification file should be compiled in a Word or Excel document (see Supplementary Material for examples). The file must contain two distinct tables, either in separate Word pages or Excel sheets: the General Table and the Event Table. The General Table comprises a listing of the expected non-study specific variables (i.e., those listed in Table 1), along with their description, data type (e.g., numeric, string, date, and time), derivation, label, and more (Table 2). It can also contain optional elements specifying whether the described variable is required or not for inclusion in the dataset and/or whether it needs input from the pharmacometrician following each data update.

TABLE 2 Structure of the specification file general table.

Name	Label	Type	Comments	Required (optional)	Pharmacometrician input (optional)
The name of the variable (e.g., USUBJID, STUDY, TIME)	Description of the variable (e.g., Subject ID, Study name, Actual time of assessment)	The type of variable (e.g., numeric, string, date-time)	Comments regarding the variable and its derivation (e.g., the unique subject ID should be composed of the study name plus a serial number, separated by dashes)	Whether this variable's inclusion in the dataset is required or optional	Whether a pharmacometrician's input and review is required for the variable after each data update

TABLE 3 Structure of the specification file event table.

NAME	VALUE	VALUETXT	UNIT	TYPENAME	LLOQ	ULOQ
Name of the event	Indicates whether the observed event is numeric (i.e., "[Num]"), or otherwise defines the numeric mapping of the event's text values	If the VALUE is not numeric, the categories for the event	Unit of measurement of the event (if applicable)	Type of the event (Dose, PK, PD, covariate, adverse event, etc.)	Lower level of quantification of the event (if applicable)	Upper level of quantification of the event (if applicable)

Abbreviations: PD, pharmacodynamic; PK, pharmacokinetic.

"Event" refers to a row in the two-dimensional dataset, distinguished by its NAME and VALUE/VALUETEXT, which can reflect the dosing, PK concentrations, PD observations, efficacy or safety readouts, baseline or time-dependent covariates, adverse events, co-medications, or any other relevant observation. The "Event Table" consequently describes the various events in the dataset, accompanied by their description, values, units, and, when applicable, limits of quantification (Table 3).

After the specification file has been uploaded, the app will check that all the necessary fields exist in both specification tables and will notify the user otherwise (Figure S2). The user can then select the variables to examine from the General Table and filter out any optional variables or those which do not require input from a pharmacometrician. For each selected variable, the app will display relevant summaries, such as their unique values, data type, and number of missing values. The selected variables can be compared against their definition in the specification file, presented in a separate table. If a selected variable does not exist in the dataset, it will be highlighted in red and appear in italics in the selection box (Figure 4). For ease of use, the app will highlight variables or events that contain missing values in yellow and any inconsistencies (e.g., multiple units for the same variable) in red. The example in Figure 4 shows that VALUE contains two missing values and is highlighted in yellow. As this column pertains to the Event Table, the user can select the option to switch to it ("Switch to event table"). This allows for comparison of the relevant events with their definition in the specification file, making sure that no missing values exist and that the units for each event are correct. The example in Figure 5 shows that both the "Plasma Concentration Z" and "Efficacy Marker" events are highlighted in yellow and each have one missing value. As these two events require reporting or further review, they can be selected by clicking on their corresponding row in the comparison table, which reveals three options:

1. The "Review NA Rows" button will prompt a pop-up window which will display the rows in the dataset where the missing values were detected. This will enable the user to more accurately report the location of the issue. The example in Figure S3 shows that there are two rows where VALUE is empty, that both of them relate to the same subject (ZY100101109) and that they occurred in the third and eighth visits. These insights can be part of the QC Report and assist the programmer in locating and resolving the issues in the data.
2. Selecting two or more values will allow the user to compare them against each other, via the "Compare and align variables" button. This feature is useful for making sure that associated variables match as expected and that their corresponding values are correct (e.g., ensuring that each NAME is matched with a correct TYPENAME).
3. If any event or variable was found to be erroneous, the user can add it to their QC Report via the "Add selected variables to QC report" button.

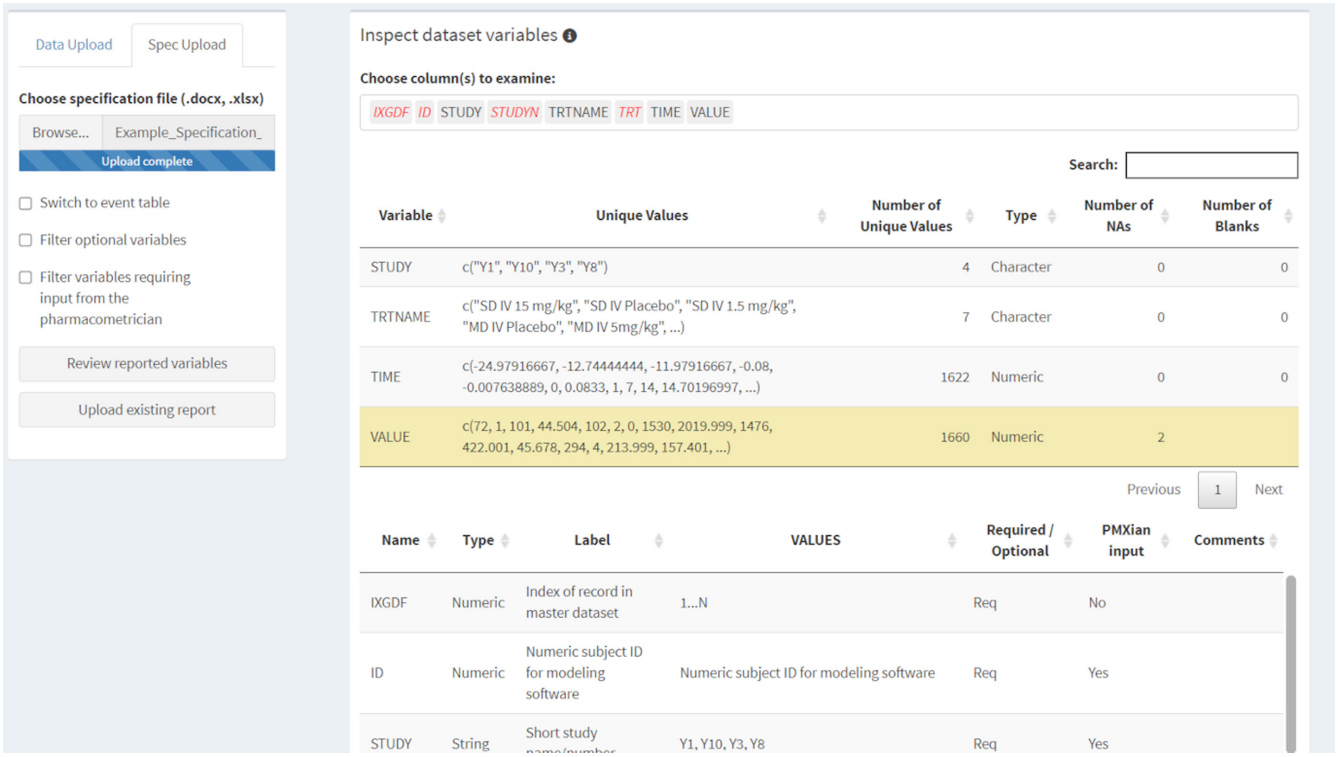


FIGURE 4 Comparing the dataset to the general specification table. In the top table, selected variables will be displayed with a summary of their unique values, type, and amount of blank or NA values in the dataset. Variables that have any missing values will be highlighted in yellow. In the bottom table, each selected variable's description from the specification file is presented for comparison with the dataset. NA, missing or unavailable.

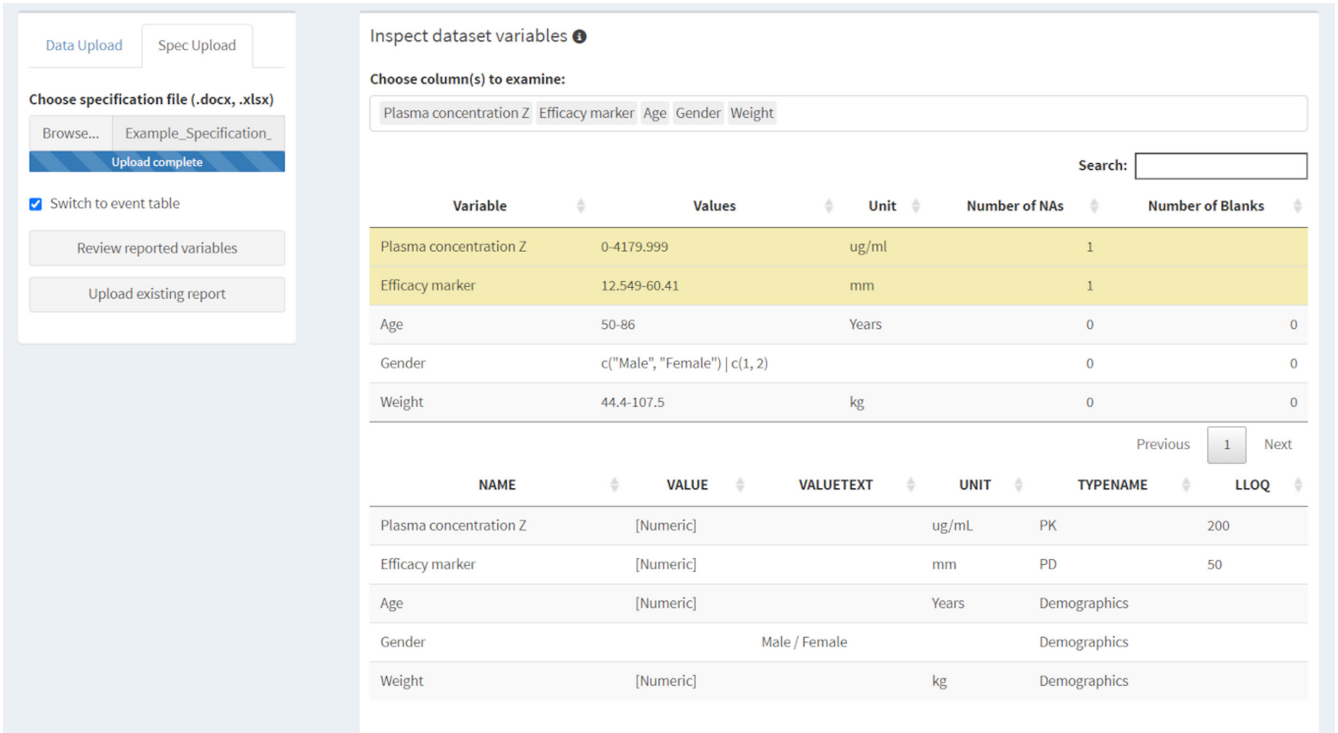


FIGURE 5 Reviewing the event table. Similarly to the General Table, selected events will be displayed in the top table and compared with their specification and missing values will be highlighted in yellow.

The user can click on the "Review reported variables" button to pull up an interim summary of the QC Report. The reported variable names will be displayed in tabular view, and the user can fill in the respective "Comments" field by double-clicking on each table row. Once all the relevant values and comments have been added to the QC Report, the user may move on to the next step in the QC workflow: performing visual and summary checks.

CONDUCTING VISUAL INSPECTION AND REVIEWING SUMMARY DATA

The sidebar titled "Visualization" features tabs "Graphical Exploration" and "Summary Tables." The "Graphical Exploration" tab consists of a plethora of plots categorized as follows: (Figure 6):

- Observations:
  - "Spaghetti" plots display changes in a selected observation over time. A separate line for each individual participant in the same plot allows for detection of missing or abnormal values. The user can also enable the "Focus on individual profiles" option which will split the selected observation by cohort and participant. This option allows the user to examine individual trends in the dataset more closely and notice missing values. The example in Figure S4 shows that the concentration profile for subject ZY300505010 in the MD IV 5 mg/kg arm is constantly decreasing despite being in a multiple dosing cohort. That subject can be added to the QC Report by double-clicking on their individual plot. Each recorded issue can be supplemented with comments, as shown in previous section.
  - "Median Range" plots display the median and confidence interval across participants for the selected observation. This and the previous plot types are stratified by treatment arm by default and can also be stratified by a chosen time-independent covariate.
  - "Individual" plots allow for selection of participant identifier and display their observations over time.
- Covariates:
  - "Covariate Distribution and Correlation" plots are divided into "Categorical" and "Continuous", and display the distribution of the covariates and their correlations accordingly. This is useful for ensuring that covariate values are within the expected range and match expectations (e.g., body mass index and body weight are positively correlated);
- Timings:
  - "Nominal vs. Actual Time" plots display three graphs which assist the user in ensuring that these two time variables are consistent:
    - Scatterplot of protocol-defined NT versus actual time, with correlation line.
    - Scatterplot of the difference between nominal and actual time versus actual time.

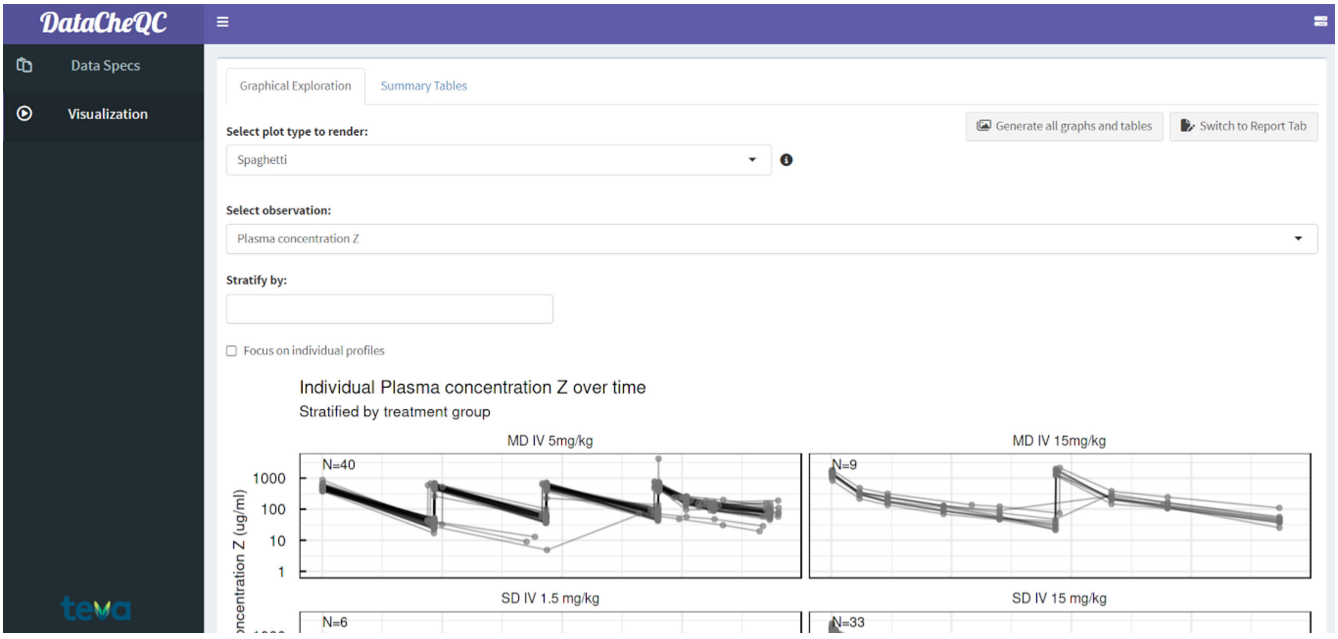
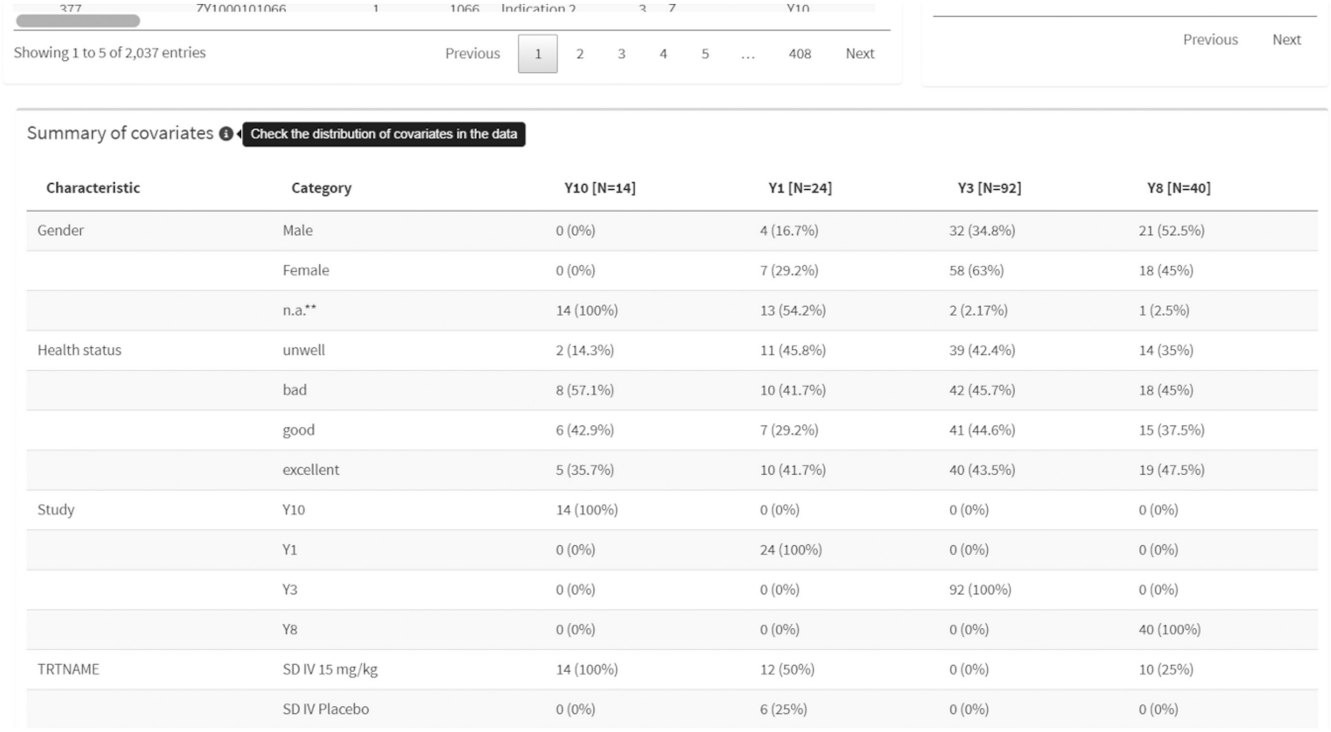


FIGURE 6 The graphical exploration tab. Once the dataset has been processed, the user can view several types of visualizations for each observation, as well as stratify them by a selected time-independent covariate. The information displayed when hovering over the info icon will change according to the selected plot type. The button labeled "Generate all graphs and tables" will initiate download of all available plot types and summary tables as a .zip file, whereas the "Switch to Report Tab" button will bring the user back to the screen seen in the previous figures.



Characteristic	Category	Y10 [N=14]	Y1 [N=24]	Y3 [N=92]	Y8 [N=40]
Gender	Male	0 (0%)	4 (16.7%)	32 (34.8%)	21 (52.5%)
	Female	0 (0%)	7 (29.2%)	58 (63%)	18 (45%)
	n.a.**	14 (100%)	13 (54.2%)	2 (2.17%)	1 (2.5%)
Health status	unwell	2 (14.3%)	11 (45.8%)	39 (42.4%)	14 (35%)
	bad	8 (57.1%)	10 (41.7%)	42 (45.7%)	18 (45%)
	good	6 (42.9%)	7 (29.2%)	41 (44.6%)	15 (37.5%)
	excellent	5 (35.7%)	10 (41.7%)	40 (43.5%)	19 (47.5%)
Study	Y10	14 (100%)	0 (0%)	0 (0%)	0 (0%)
	Y1	0 (0%)	24 (100%)	0 (0%)	0 (0%)
	Y3	0 (0%)	0 (0%)	92 (100%)	0 (0%)
	Y8	0 (0%)	0 (0%)	0 (0%)	40 (100%)
TRTNAME	SD IV 15 mg/kg	14 (100%)	12 (50%)	0 (0%)	10 (25%)
	SD IV Placebo	0 (0%)	6 (25%)	0 (0%)	0 (0%)

FIGURE 7 Summary tables. The user can review summary statistics (e.g., an overview of the covariates and their distributions). Each table has an info icon that can assist the user in understanding the presented data.

- Histogram of the absolute difference between nominal and actual time.
  - "Dosing and Sampling Schedule" plots show the timeline of dosing or sampling of observations for each participant, and are useful for detecting missing doses and other anomalies.

Users can learn more about each plot by hovering on the info icon next to the plot type selection box.

The "Summary Tables" tab features various tables that present a summary of observations and continuous and categorical covariates, a table indicating potentially duplicated time entries, along with an interactive table representing the loaded dataset that is searchable and paginated. The example in Figure 7 shows the covariate summary table, which indicates that one of the studies (Y10) does not have any weight or gender observations. However, this may be intentional – if, for example, the Study was only conducted on males with the same weight.

The user can view all the outputs in the "Visualization" section as separate files, and download an aggregated archive (.zip file) of all the plots and summary tables via the "Generate All Plots and Tables" button.* Alternatively, the user can download the most recent plot that was displayed via the button on the top right header and choosing the preferred file format (.png, .svg, or both as a .zip archive, as shown in Figure S5).

Once the user completes the final review and visual inspection, they can begin to work on generation of the QC Report, which can be accessed via the "Switch to Report Tab" button.

QC REPORT GENERATION

By selecting "Review reported variables", the user can review ongoing QC findings (Figure S6). The table with variables has a "Status" field, to capture any updates from the programmer after implementing the requested changes. The user can choose which components to include in the QC Report:

1. Data specification review
2. A table of outlying participants
3. Plot of individual profile over time for an outlying participant.

In order to maintain traceability of the QC Report, the user must include their name in the appropriate text input field. The user can then download the generated report file, which will contain their chosen elements along with

*Plots will be included as .pdfs and tables will be included as .txt files, along with .log files that document the time when the files were created and their origin. This operation is performed asynchronously so all users may continue using the app's other features while the download is in progress.

Z QC Findings Report
Generated 02/04/2023, 7:46 EDT
Prepared By: Or Dotan

Variable	Comments	Status
Efficacy marker	NA values for Subject ZY100101109 at Visits 3 and 8	
Plasma concentration Z	NA values for Subject ZY100101109 at Visits 3 and 8	

Flagged Subject List

Subject	Observation	Treatment Arm	Comments
ZY300505010	Plasma concentration Z	MD IV 5mg/kg	Subject seems to have missing doses

Flagged Subject Plots:

ZY300505010 - Plasma concentration Z - MD IV 5mg/kg

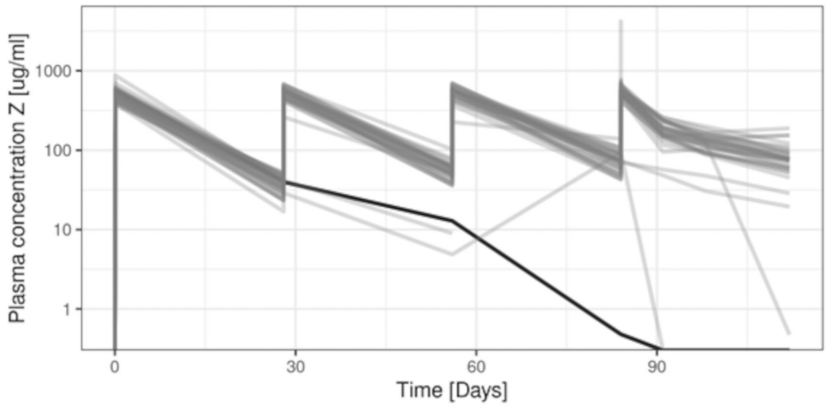


FIGURE 8 The QC Report. After compiling all findings in the Report tab, and clicking on the "Save report" button, a .docx file will be downloaded. The file includes a timestamp, author's name, and tables displaying the reported variables or subjects and respective comments. In case there were individual profiles that require further review, the user can also include a plot of their-time profile in the QC Report. QC, quality control.

their name and a timestamp, via the "Save report" button (Figure 8).

Additionally, the user can save their work by generating a QC Report as outlined above and continue compiling their findings into the pre-existing QC Report document at a later date. This can be achieved by uploading the generated interim QC Report onto the app via the "Upload existing report" button. It should be noted, however, that doing so will overwrite any previous work done with the QC Report in the current app session.

DISCUSSION

By utilizing the interactivity and speed of Shiny apps, the entire QC process for pharmacometrics datasets can potentially become more accessible and streamlined. Visual representation of complicated and large datasets can facilitate error detection and reporting, and thus potential issues can be corrected more efficiently. Although use of the app requires adherence to certain format requirements for both the dataset and the specification file, these requirements are similar to the requirements of other NLME analysis software. However, this does not guarantee that a dataset that passes QC using the app is "ready for modeling". The scope of the app is defined to prioritize checking for issues within the dataset and compare the dataset against its corresponding data specification file. Consequently, there are still some features which can be introduced in future to expand the app's capabilities, such as:

- Checking the data for compatibility with the most common NLME software platforms
- Additional plot types as part of data visualization
- Handling alternative data specification file types

As part of the efforts to address these future functionalities and keep improving the app, DataCheQC is freely and publicly available under the terms of the GNU General Public License.[23] This approach is in line with the principles of open-source science, which prioritize transparency and accessibility, and encourages discussion and

cooperation. Seeing as increased collaboration can lead to progress and innovation, users are encouraged to contribute suggestions and comments to this project. The app can be accessed online via shinyapps.io (https://dotanor.shinyapps.io/DataCheQC/) and its source code is available on GitHub (https://github.com/DotanOr/DataCheQC).

CONCLUSION

Creating simple, comprehensive tools to improve and enhance pharmacometrics workflows can lead to better and more efficient drug research and development. In particular, the use of Shiny apps in the QC of pharmacometrics datasets has the potential to streamline and improve the data analysis process for all users, regardless of their background. DataCheQC's interactive features and visual representations were created to facilitate efficient error detection and reporting, as well as highlight issues that would have otherwise gone unnoticed. The app's public availability under an open-source license aims to encourage collaboration and discussion for the purpose of app's improvement. The authors believe that this application has the potential to become a helpful asset for conducting QC and assurance of data validity, simplifying the potentially lengthy process of QC into a more efficient task.

AUTHOR CONTRIBUTIONS

O.D. and A.R. wrote the manuscript. O.D. and A.R. designed the research. O.D. performed the research. O.D., A.R., and R.S. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

O.D. is an employee of Teva Pharmaceutical Industries. A.R. is the owner of intiGROWTH LLC, Miami, FL, USA. R.S. is an employee of Teva Pharmaceutical Industries. Authors O.D and A.R were paid as consultants of Teva Pharmaceutical Industries.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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